

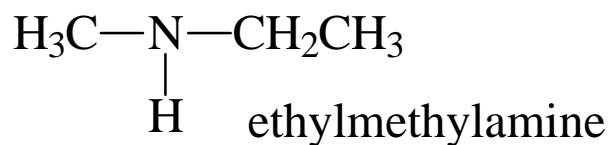
# Amines

Nomenclature —

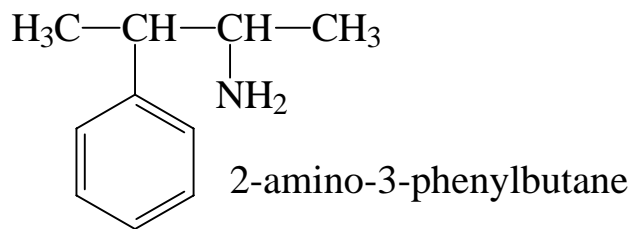
1°:  $\text{RNH}_2$ , 2°:  $\text{RR}'\text{NH}$ , 3°:  $\text{RR}'\text{R}''\text{N}$ , 4° (salt)  $\text{RR}'\text{R}''\text{R}'''\text{N}^+$

R = alkyl or aryl

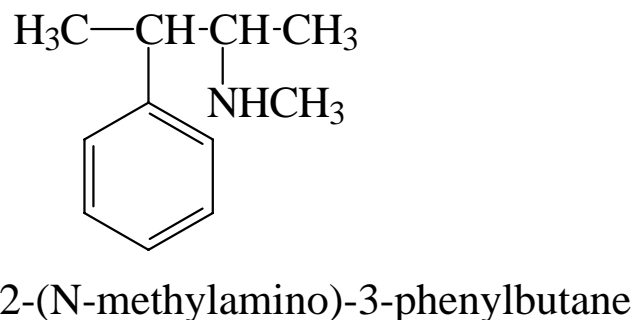
For aliphatic amines  
name groups attached to  
N; use suffix -amine.



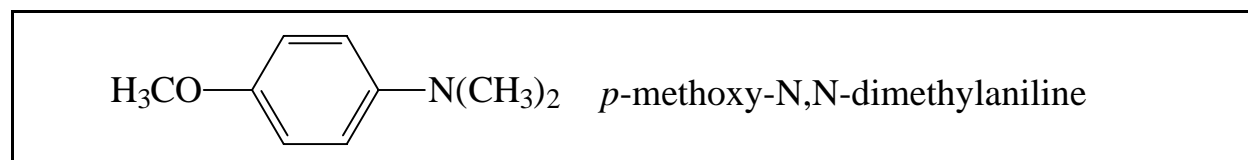
In complicated structures  
the prefix amino- may be  
used.



Substitution on nitrogen  
is indicated by an  
uppercase N.



Aromatic amines are often named as derivatives of aniline,  $\text{Ph-NH}_2$ .

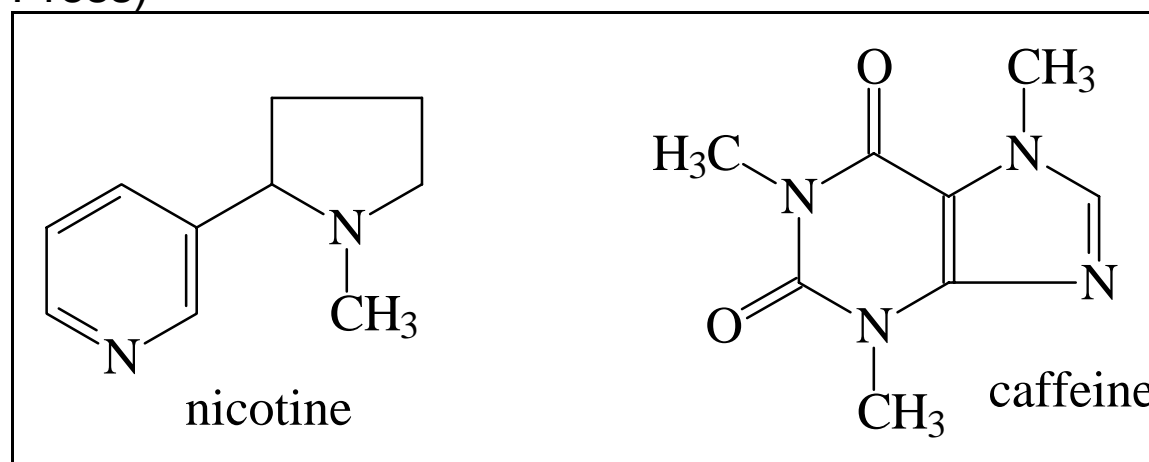


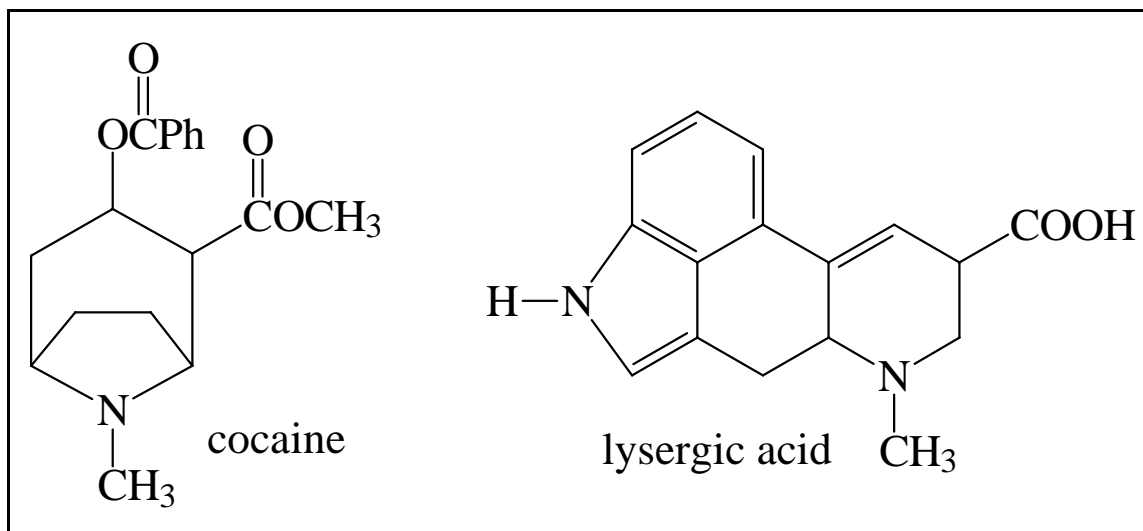
Low molecular weight amines have fishy odors and in some cases may be quite unpleasant smelling. Two amines, found in rotting flesh, are named for their unpleasant odors —

$\text{H}_2\text{N}(\text{CH}_2)_4\text{NH}_2$ , putrescine,

and  $\text{H}_2\text{N}(\text{CH}_2)_5\text{NH}_2$ , cadaverine.

"Alkaloids" are basic nitrogenous plant products.  
(Reference: Manske & Holmes, "The Alkaloids," Academic Press)





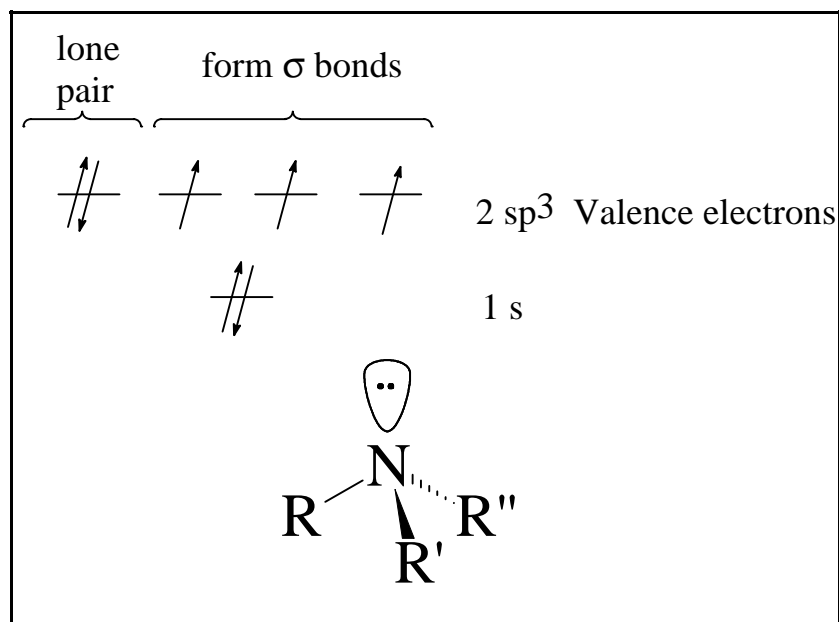
## Stereochemistry of N in Amines —

$sp^3$  hybrid -  
7 electrons.

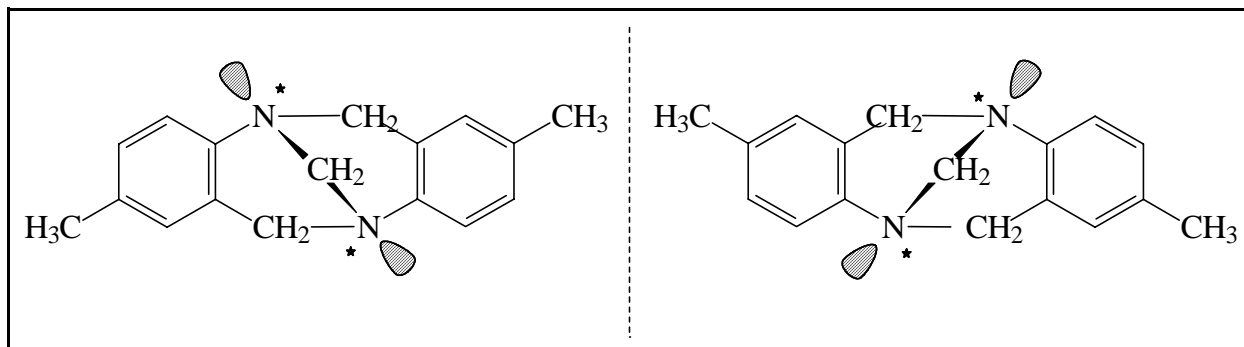
Molecules of this type, with 3 different groups attached to N should show stereoisomerism (enantiomers). We rarely see this, however,

because of rapid inversion of the configuration around the nitrogen: the lone pair switches from one side of the nitrogen to the other and back again rapidly.

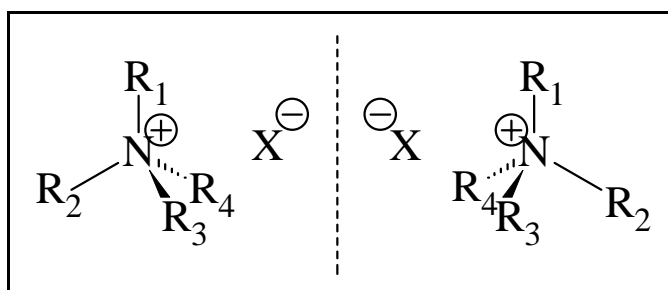
Consequently, usually the two configurations cannot be isolated.



Troger's base is an exception where resolution has been successful.



In the case of quaternary ammonium salts enantiomers can be resolved —



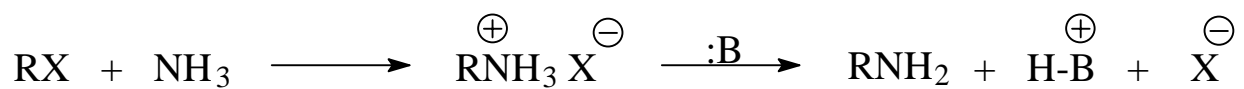
## Preparation of Amines —

Reduction of Nitro Group —

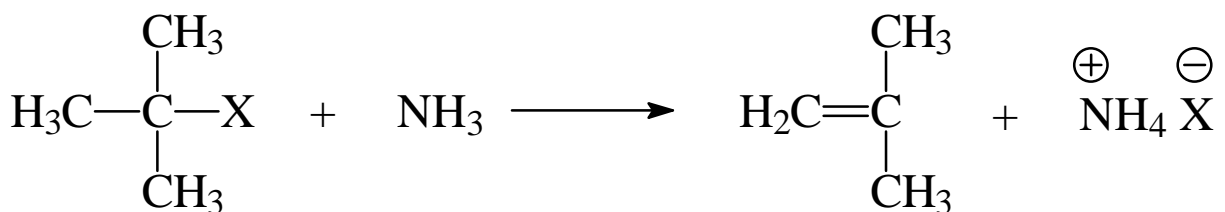
For aromatic amines, reduction of a nitro group is a common method. (Although this method works for aliphatic compounds, the nitro group is less common in these compounds.)



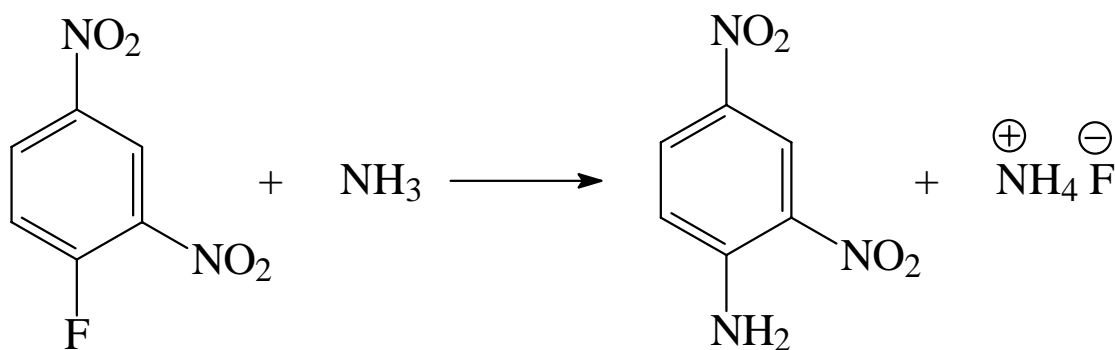
## Ammonolysis of Halides —



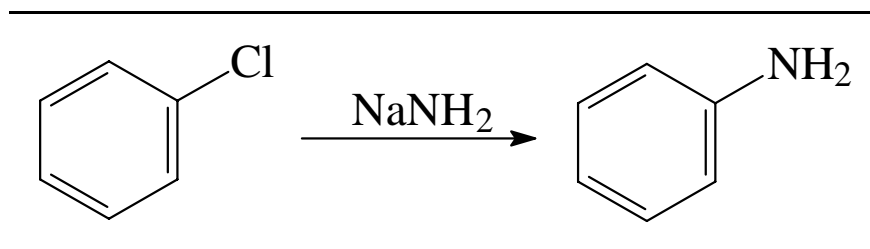
This reaction works best for 1° alkyl halides and may work for 2° halides, but for 3° halides —



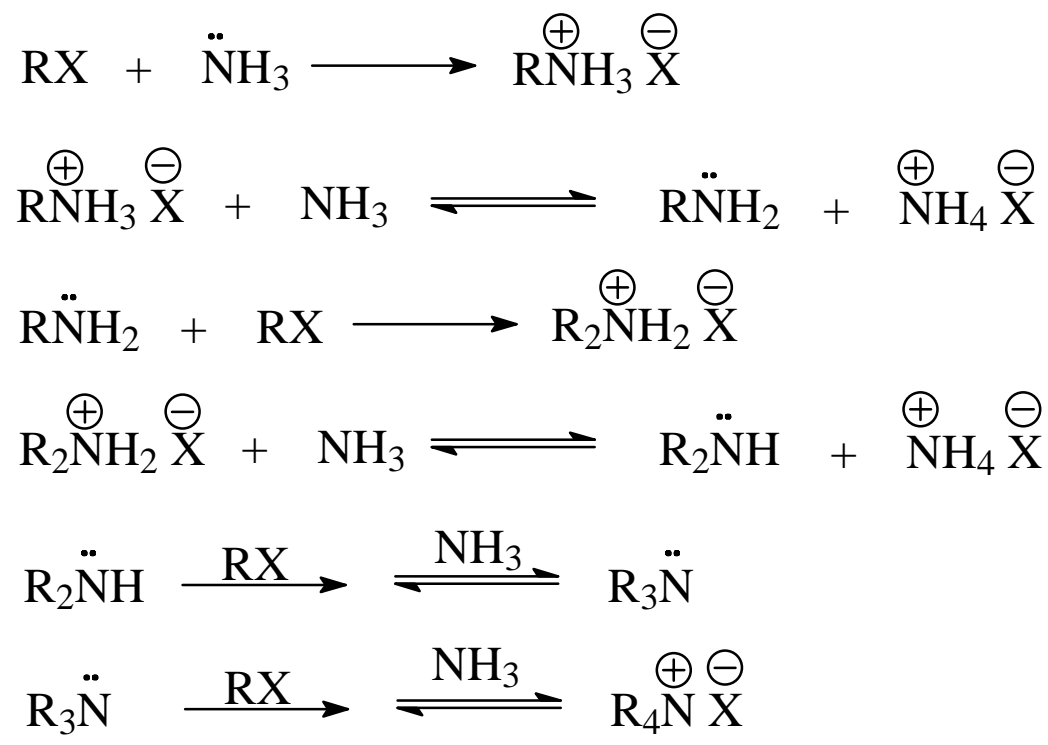
Vinyl and aryl halides do not usually react. Aryl halides will react if strong electron withdrawing groups (activating for *nucleophilic* aromatic substitution) are located ortho or para to the halogen —



or if a strong nucleophile is used (*via* an elimination-addition involving benzyne) —

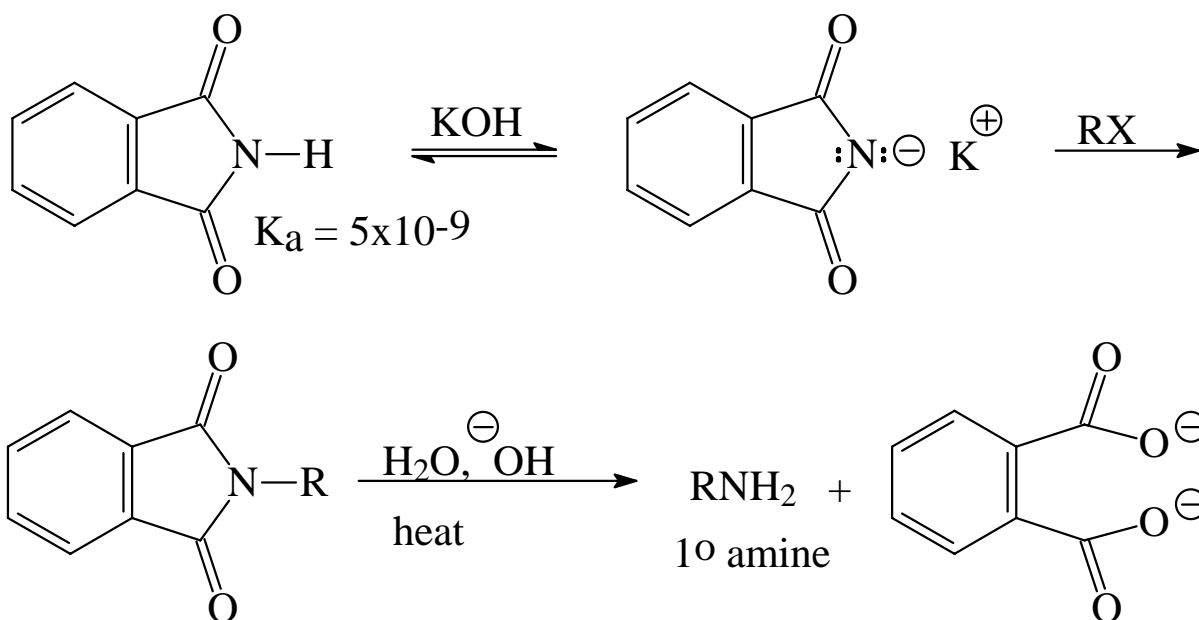


A severe limitation to ammonolysis in many cases is generation of other classes of amines —



The Gabriel Synthesis —  
for preparation of pure 1° amines.

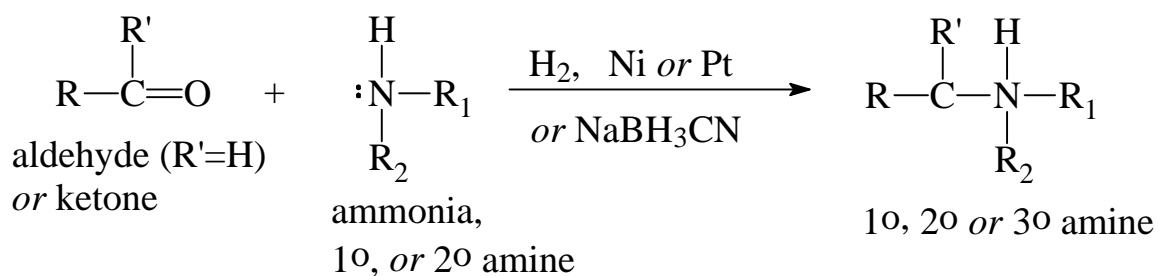
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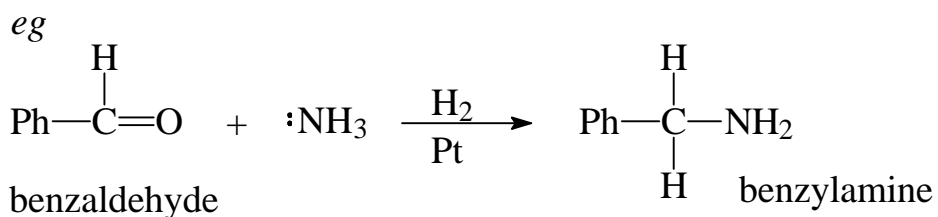
Preparation of Amines *via* Reduction —

\* A. Reductive Amination.

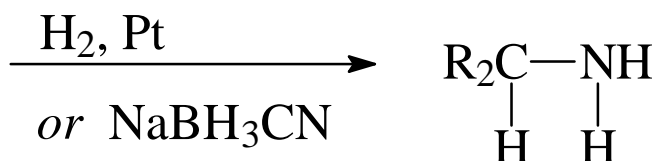
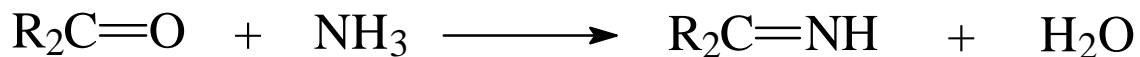
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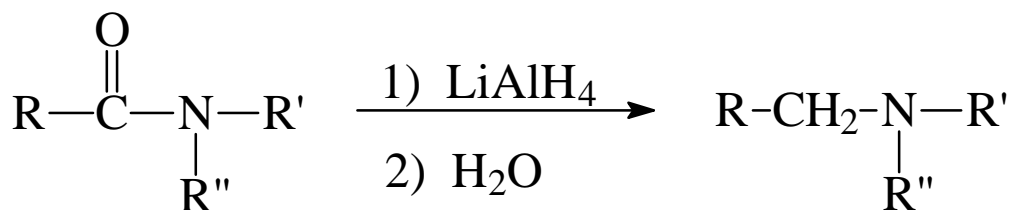
Rs may be Ars



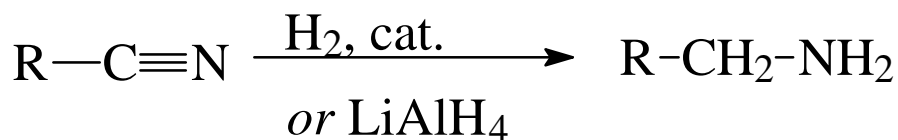
In forming 1° and 2° amines, the reaction probably proceeds through an imine:



✱ B. Reduction of Amides —



✱ C. Reduction of Nitriles —

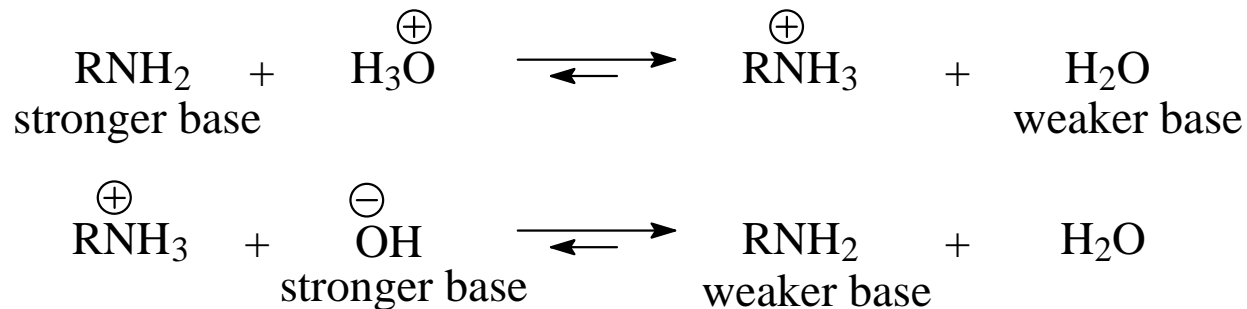




## Reactions of Amines —

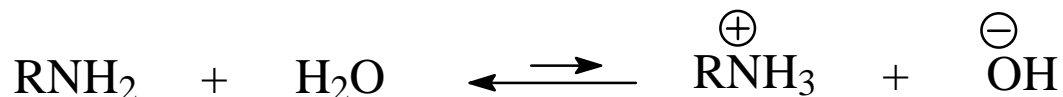
### Basicity of Amines —

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On a quantitative basis we may measure the basicity of an amine by its ability to accept a proton from water.

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$$K_b = \frac{[\text{RNH}_3^{\oplus}][\text{OH}^{\ominus}]}{[\text{RNH}_2]}$$

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Factors which stabilize the ammonium ion,  $\text{RNH}_3^+$ , compared to the amine,  $\text{RNH}_2$ , will increase  $K_b$ ; factors which destabilize the ammonium ion compared to the amine will decrease  $K_b$ .

[Sometimes the basicity of an amine,  $\text{RNH}_2$ , is reported by giving the  $K_a$  of its protonated form,  $\text{RNH}_3^+$ . This  $K_a$  and  $K_b$  are inversely related.]

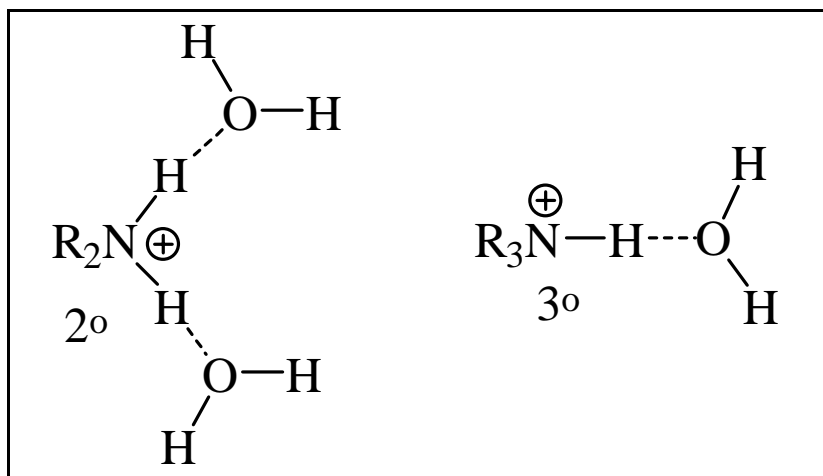
Therefore, one might expect the following order of basicity in amines:

$R_3N: > R_2HN: > RH_2N: > H_3N:$ ,  
but the following is observed:

$pK_b$	$MeNH_2$	$Me_2NH$	$Me_3N$
	3.36	3.23	4.20
$NH_3$	1° amine	2° amine	3° amine
4.75			
ammonia	$EtNH_2$	$Et_2NH$	$Et_3N$
	3.33	3.07	3.12

So, the 2° amines are the most basic.

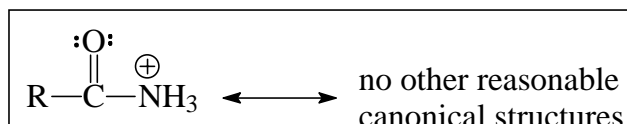
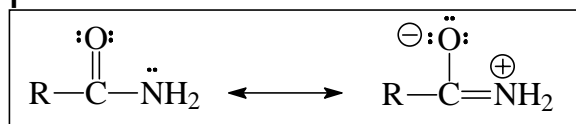
Explanation — The stability of the ammonium ion is also determined by its degree of solvation in solution. Solvation occurs via hydrogen bonding and the order of hydrogen bonding is:  $NH_4^+ > 1^\circ > 2^\circ > 3^\circ$ .



In solvents which do not hydrogen bond (eg benzene) the order of basicity is:  
 $R_3N > R_2NH > RNH_2 > NH_3$ .

## Effect of Resonance on Basicity —

Amides are not basic at the nitrogen mostly because of resonance effects. The amide is stabilized relative to the protonated amide.

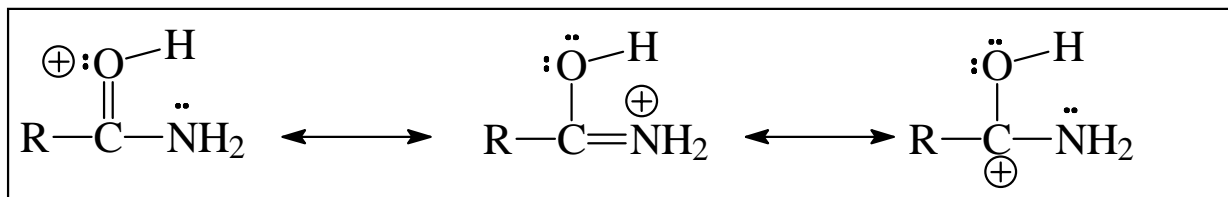
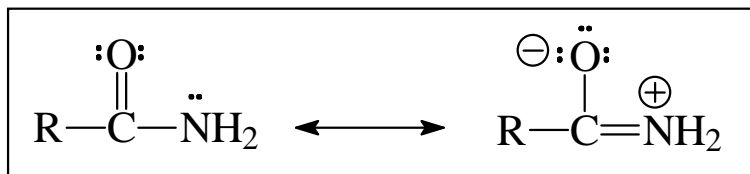


On the other hand, amides are basic at the carbonyl oxygen. This can also be explained by resonance.

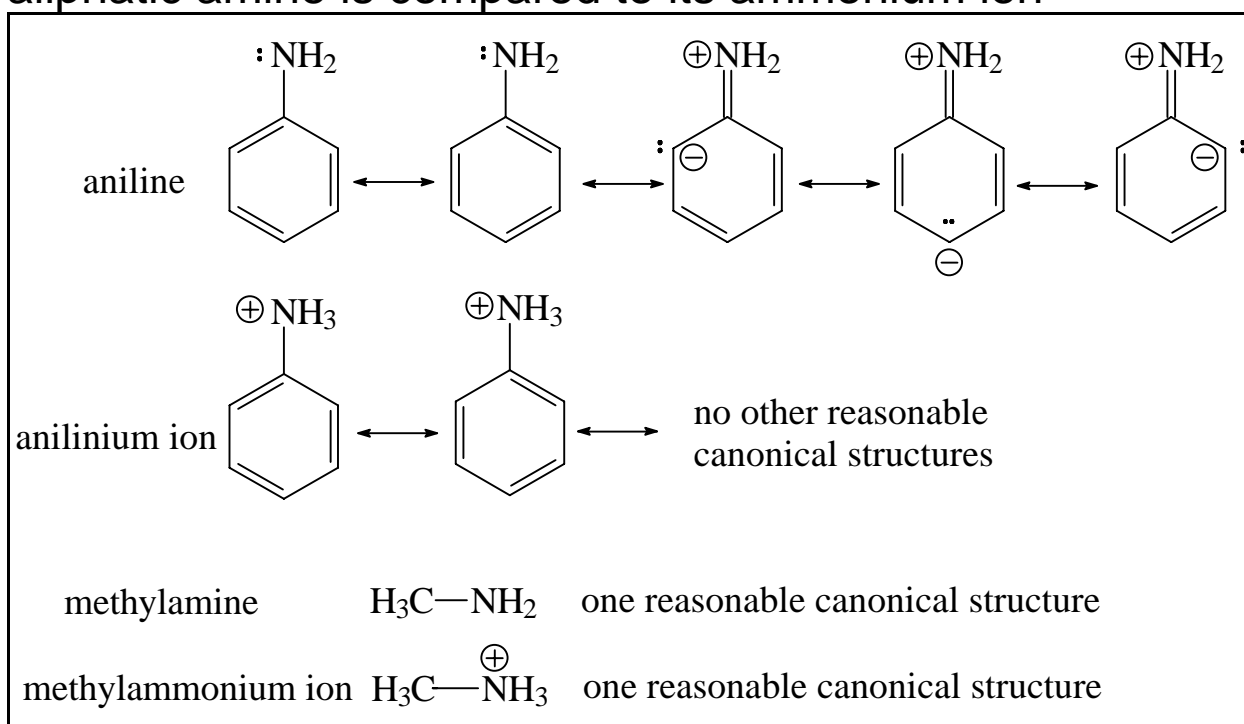
Acidities of Protonated Compounds		
Compound	Conjugate Acid	pK <sub>a</sub> of Conjugate Acid
CH <sub>3</sub> CONH <sub>2</sub>	$\text{CH}_3\overset{+\text{OH}}{\parallel}{\text{C}}\text{NH}_2$	0.0
H <sub>2</sub> O	H <sub>3</sub> O <sup>+</sup>	-1.7
CH <sub>3</sub> OH	$\text{CH}_3\overset{+}{\text{O}}\text{H}_2$	-2.2
(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> O	$(\text{CH}_3\text{CH}_2)_2\overset{+}{\text{O}}\text{H}$	-3.6
CH <sub>3</sub> COOH	$\text{CH}_3\overset{+\text{OH}}{\parallel}{\text{C}}\text{OH}$	-6
CH <sub>3</sub> COOC <sub>2</sub> H <sub>5</sub>	$\text{CH}_3\overset{+\text{OH}}{\parallel}{\text{C}}\text{OC}_2\text{H}_5$	-6.5
CH <sub>3</sub> COCH <sub>3</sub>	$\text{CH}_3\overset{+\text{OH}}{\parallel}{\text{C}}\text{CH}_3$	-7.2
CH <sub>3</sub> CHO	$\text{CH}_3\overset{+\text{OH}}{\parallel}{\text{C}}\text{H}$	~-8
CH <sub>3</sub> COCl	$\text{CH}_3\overset{+\text{OH}}{\parallel}{\text{C}}\text{Cl}$	~-9
CH <sub>3</sub> CN	$\text{CH}_3\overset{+}{\text{C}}\equiv\text{NH}$	-10.1

[In the table to the left, the most basic compound is at the top and the least basic is at the bottom. The conjugate acids of these bases are also shown, along with their pK<sub>a</sub>s. The weakest conjugate acid is at the top of the list and the strongest is at the bottom.]

As noted above, the reason for amide basicity at the oxygen can also be explained by resonance —



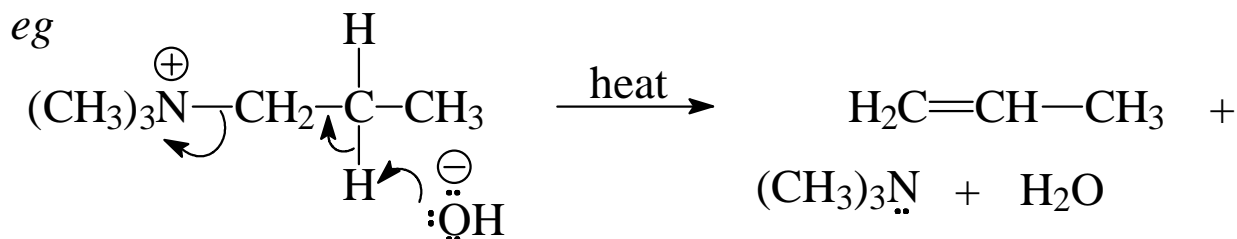
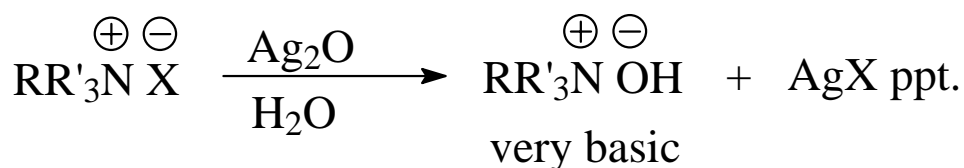
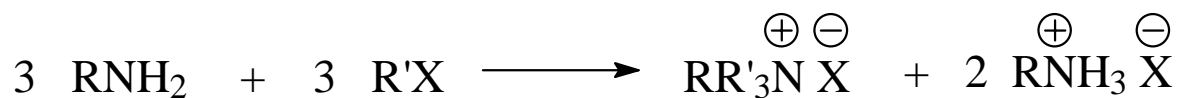
Aromatic amines are less basic than aliphatic amines, mostly because of resonance. The aromatic amine is more stabilized compared to its ammonium ion than an aliphatic amine is compared to its ammonium ion —



Compound	pK <sub>b</sub>
methylamine	3.46
aniline	9.38
diphenylamine	13.2

## More Reactions of Amines —

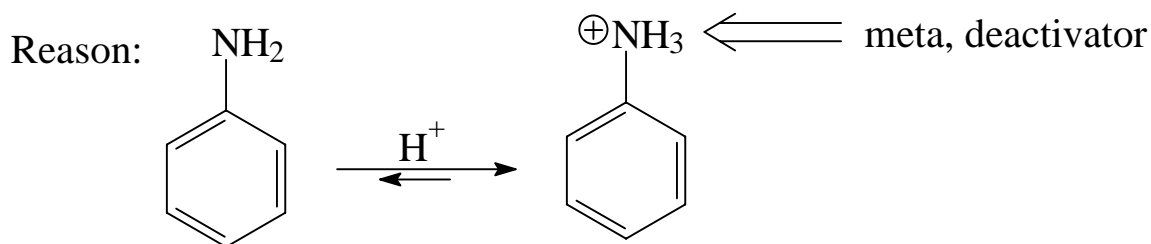
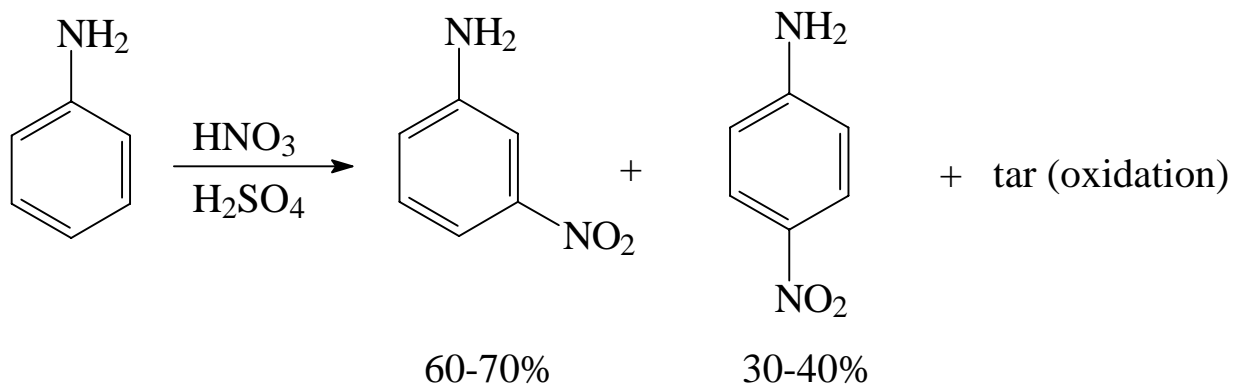
### Hoffmann Elimination Reaction —



## Nitration of Aromatic Amines —

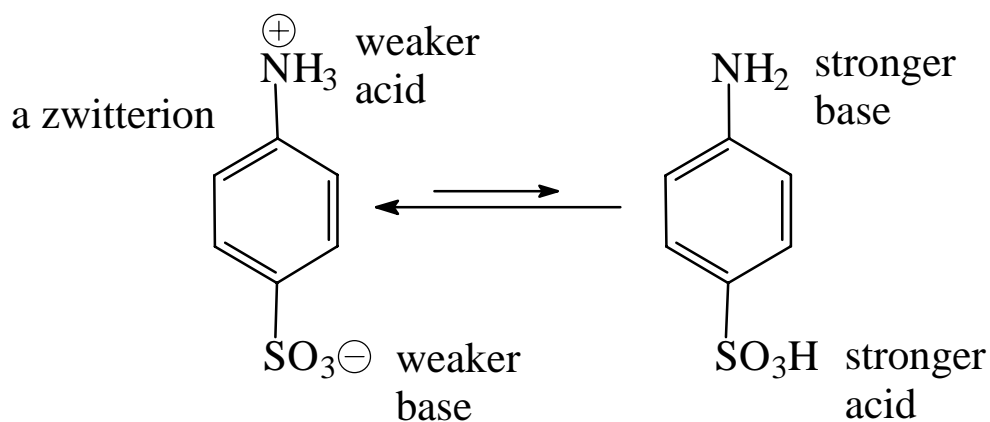
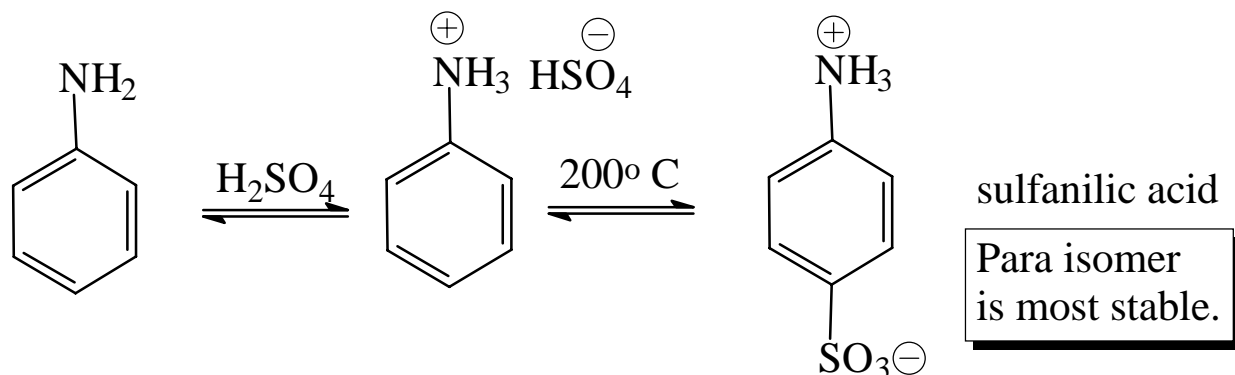
$\text{-NH}_2$  is an o, p-directing activating group for electrophilic substitution. However,

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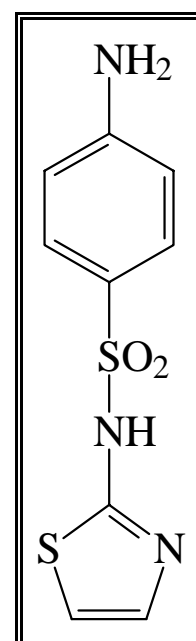
This problem can be avoided by *protecting* the amino group by acetylation, nitrating, and deprotecting the amino group by hydrolysis of the amide.

## Sulfonation of Aromatic Amines —



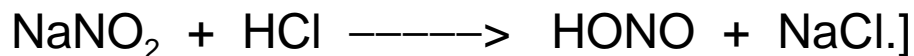
Certain N-substituted amides of sulfanilic acid, sulfanilamides, are bacteriostatic and are known as *sulfa* drugs. Sulfathiazole is shown.

Sulfa drugs were widely used as broad-spectrum antibacterials before penicillin.



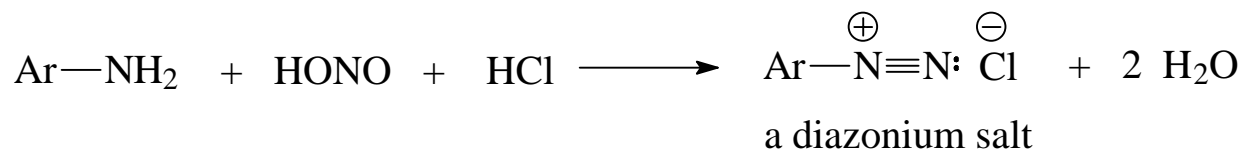
## Reactions of Amines with Nitrous Acid —

[Nitrous acid, HONO, is not stable and is generated *in situ* from an acid and sodium nitrite:



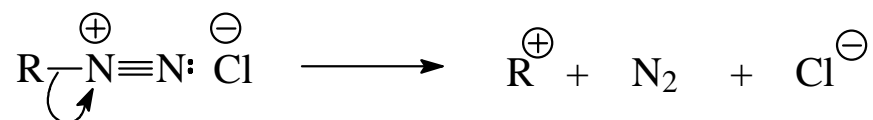
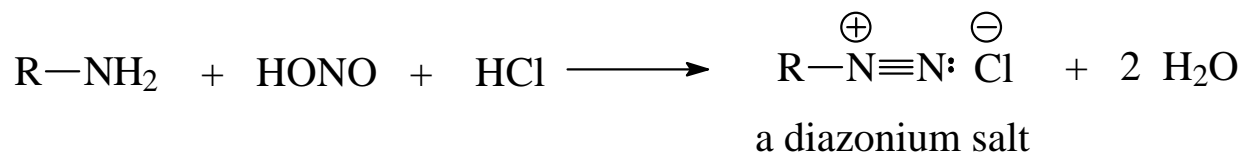
### \* Primary aromatic amines give diazonium salts —

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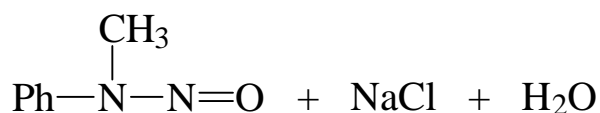
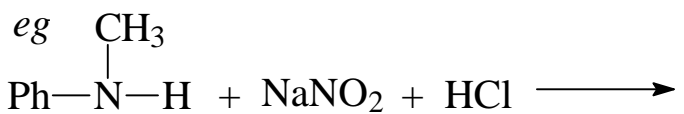
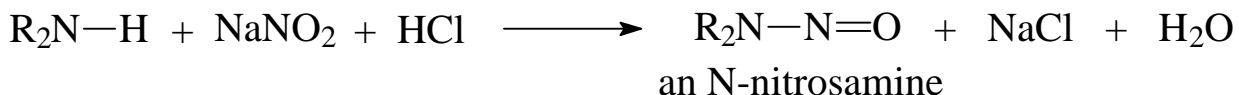
### \* Primary aliphatic amines give diazonium salts — but these compounds are unstable and decompose.

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\* Secondary aliphatic or aromatic amines give  
N-nitrosamines —

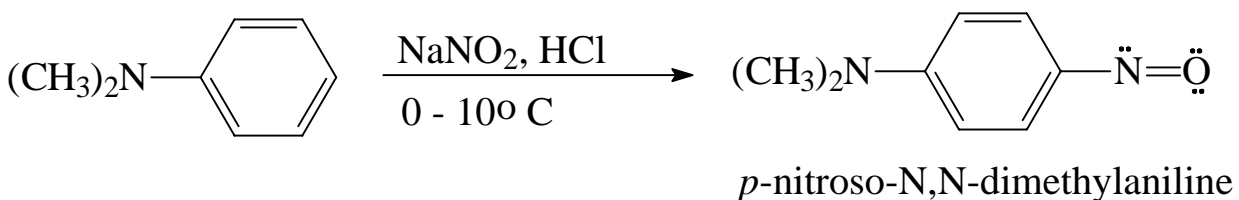


N-nitroso-N-methylaniline

CARCINOGENIC

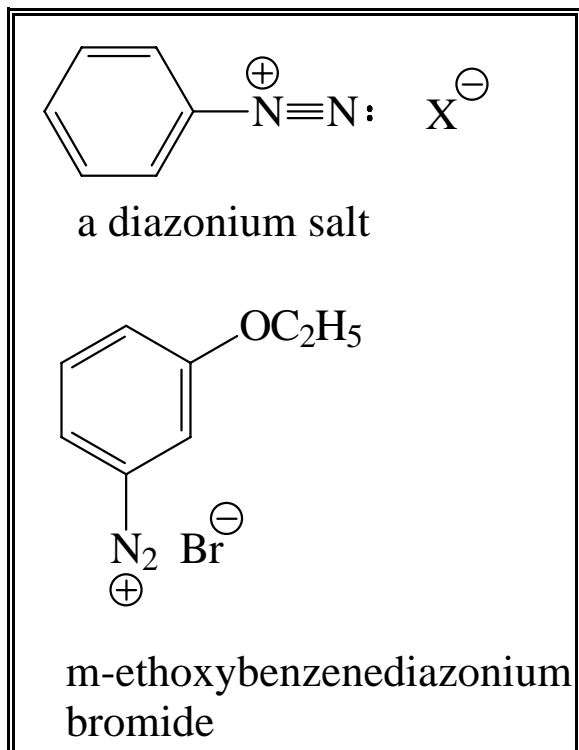
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\* Tertiary Aromatic Amines —



In all of these reactions  $^+\text{NO}$  is making an electrophilic attack. In the first two cases the attack is on nitrogen; in the last case it is on the activated ring. In each case  $\text{H}^+$  is displaced.

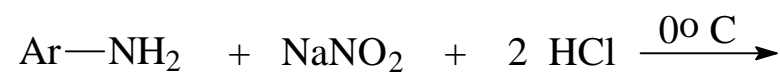
## Aromatic Diazonium Salts —



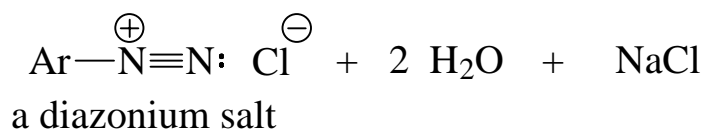
Named by adding -diazonium to the name of the aromatic compound from which they are derived, followed by the anion name.

Physical properties ---  
crystalline solids, soluble in water, explosive in solid state.

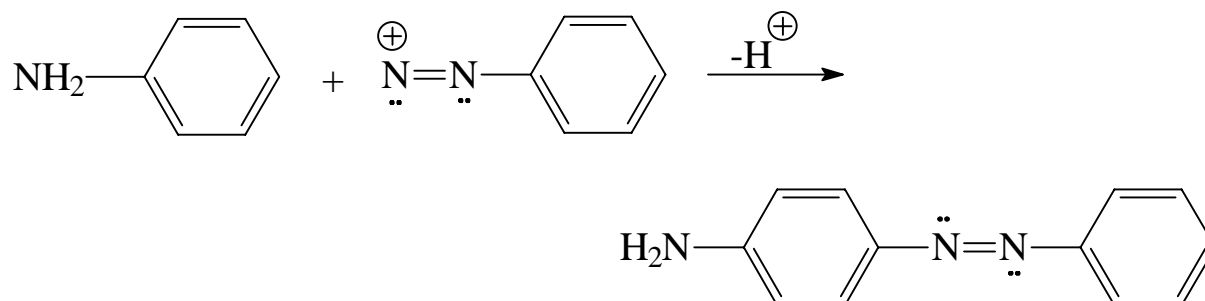
## Preparation —



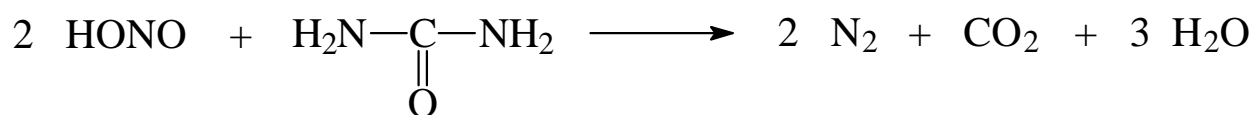
1<sup>o</sup> aromatic  
amine



Excess HCl (more than 2 equivalents) is employed to keep the reaction mixture acidic to avoid coupling of the newly formed diazonium ion with the reactive aromatic ring — Excess NaNO<sub>2</sub> is used because HONO is unstable and



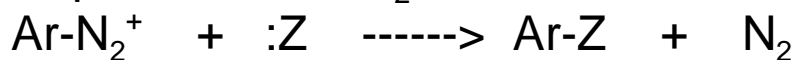
decomposes. After the diazonium salt is formed the excess HONO may be destroyed with urea —



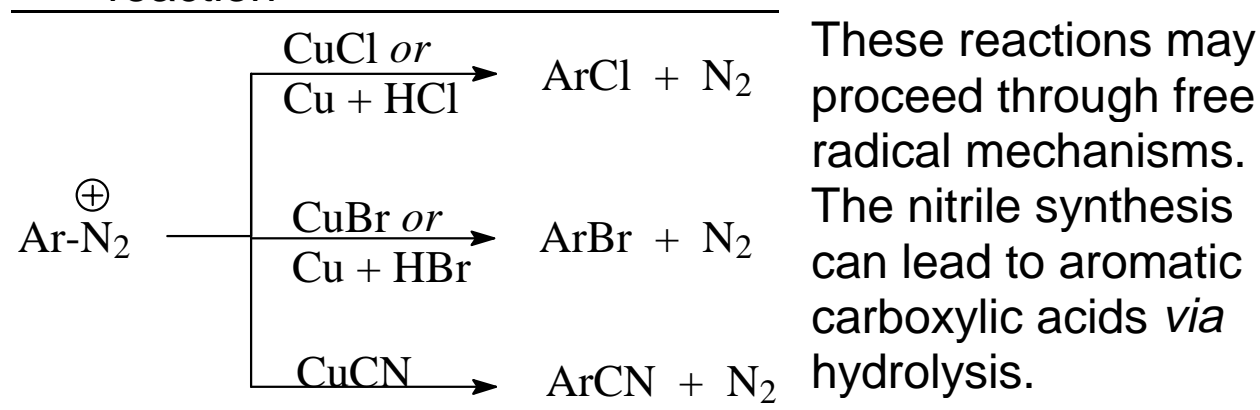
The solution of diazonium salt must be used immediately because it slowly decomposes.

## Reactions of Aromatic Diazonium Salts —

\* Replacement of  $N_2$  —



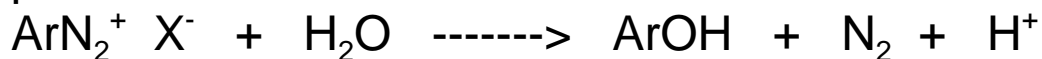
1) Replacement by -Cl, -Br, -CN: the Sandmeyer reaction —



2) Reaction of a diazonium salt with  $I^-$  produces an aryl iodide

3) and with  $\text{HBF}_4$ , an aryl fluoride.

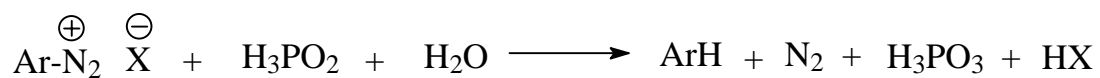
4) Aryl diazonium salts react with water to produce phenols —



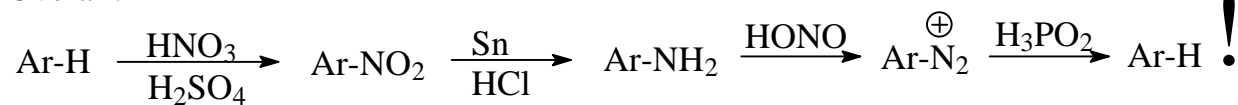
This is a side reaction whenever diazonium salts are formed in aqueous solutions.

To prepare phenols the cold solution of diazonium salt is slowly added to boiling dilute sulfuric acid. This minimizes the formation of  $\text{Ar-N=N-Ar-OH}$ . [See “coupling” below.]

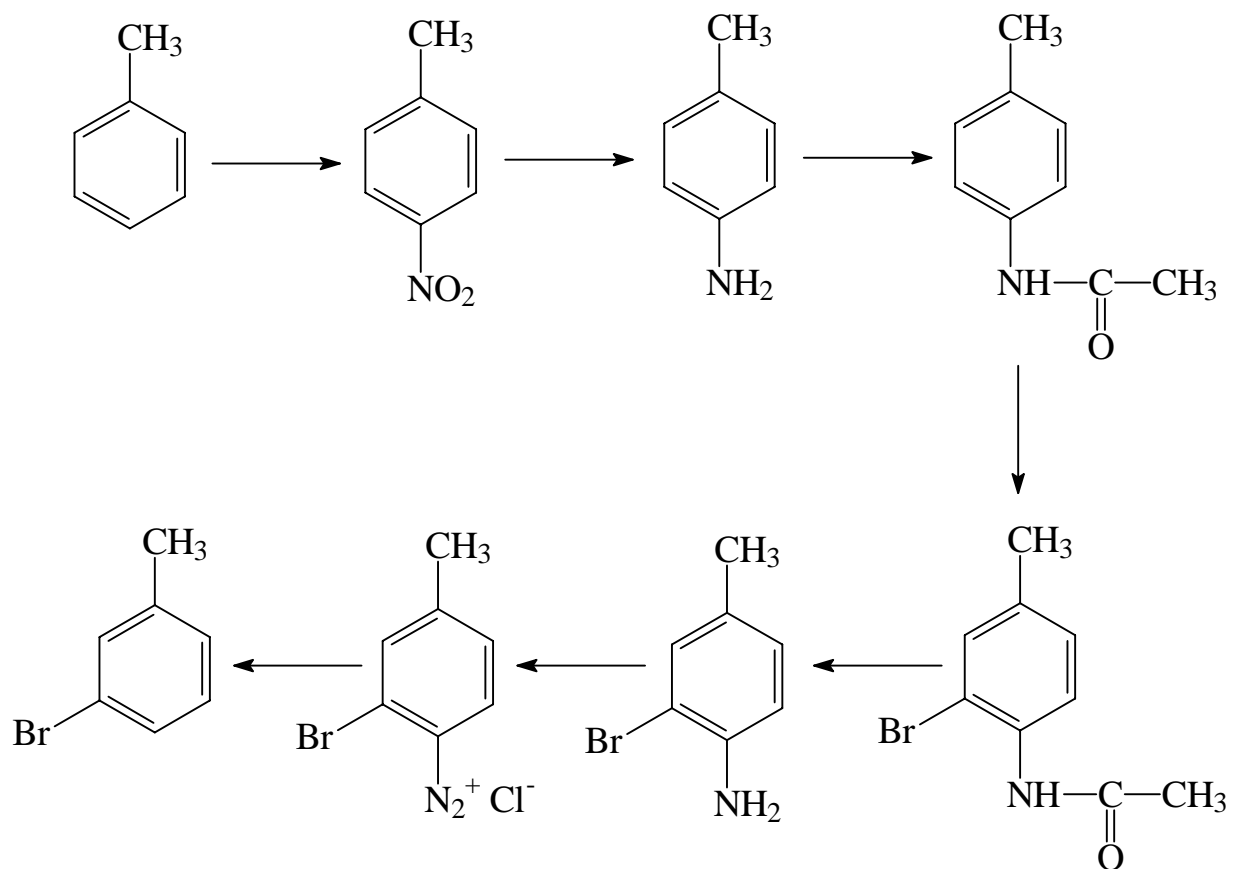
## 5) Replacement of $-N_2^+$ by $-H$ —



Overall:



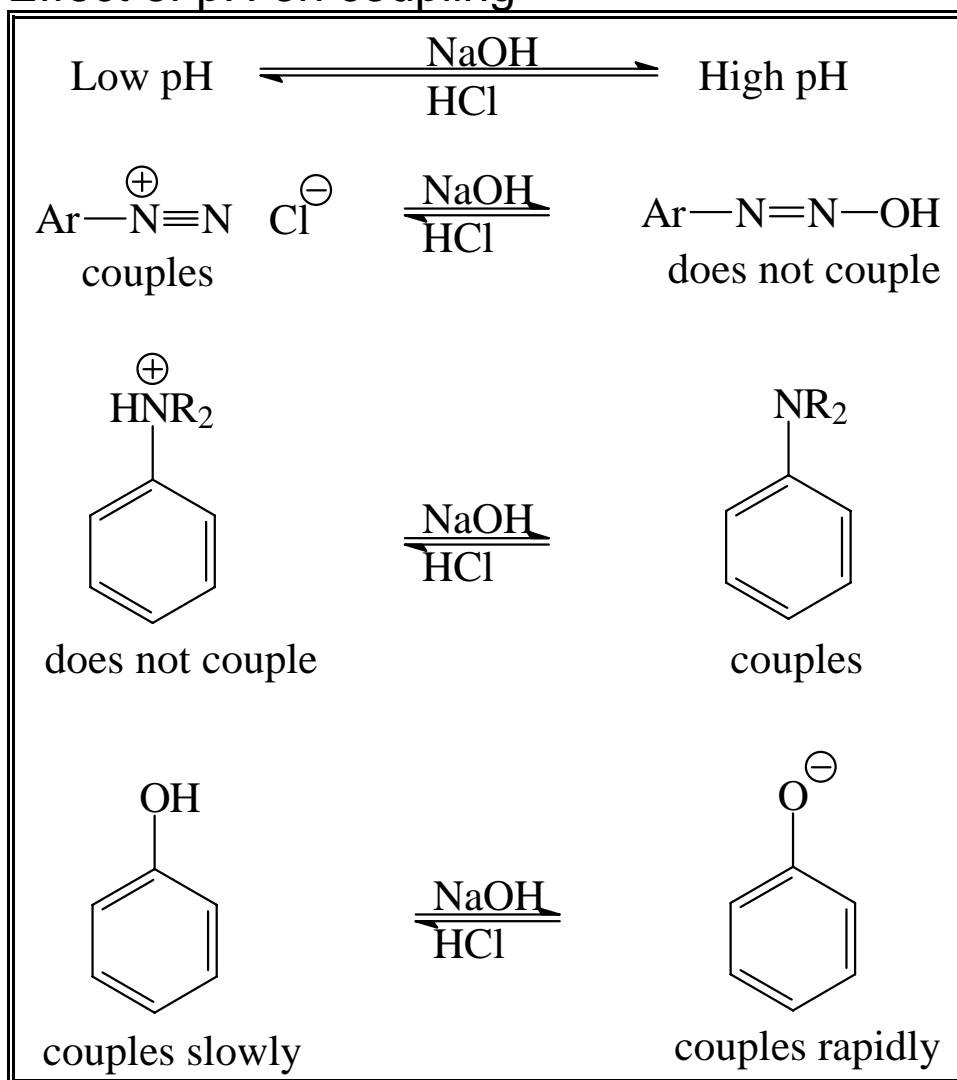
However, the  $-\text{NO}_2$  and  $-\text{NH}_2$  groups can be used for directing purposes, *eg* prepare *m*-bromotoluene —



\* Coupling — The Synthesis of Azo Compounds —

$\text{Ar-N}_2^+ \text{X}^- + \text{Ar}'\text{H} \longrightarrow \text{Ar-N=N-Ar}' + \text{HX}$   
 Usually  $\text{Ar}'\text{H}$  must contain a powerful electron releasing group eg  $-\text{OH}$  or  $-\text{NR}_2$ .

Effect of pH on coupling —



Substitution usually occurs para to the activating group. Coupling with phenols is usually carried out in mildly alkaline solution, with amines in mildly acidic solution.